Johnson & Johnson
PHARMACEUTICAL RESEARCH
& DEVELOPMENT, L.L.C.

1000 U.S. Highway 202, P.O. Box 300
Raritan NJ 08869

August 3, 2005

Dockets Management Branch (HFA-305),
Food and Drug Administration
5630 Fishers Lane, rm. 1061
Rockville, MD 20852

Re: Draft "Guidance for Industry: Safety Testing of Drug Metabolites," released for comment on June 3, 2005. (Docket No. 2005D-0203)

Dear Sir/Madam:

The Johnson & Johnson family of companies ("J&J") is the world's most comprehensive and broadly-based manufacturer of health care products, as well as a provider of related services, for the consumer, pharmaceutical, and medical devices and diagnostics markets. The more than 200 Johnson & Johnson operating companies employ approximately 114,000 men and women in 57 countries and sell products throughout the world. As a leading pharmaceutical business, J&J has extensive experience in thoroughly evaluating the safety of our products from discovery through the product life cycle. The fundamental objective of J&J is to provide scientifically sound, high-quality products and services to help heal, cure disease, and improve the quality of life.

J&J appreciates the opportunity to comment on the FDA draft *"Guidance for Industry, Safety Testing of Drug Metabolites,"("MIST")* released for comment in the Federal Register (FR Doc. 05-11205, June 3, 2005. We have reviewed this guidance, both in terms of the science and the regulatory framework needed to ensure the successful implementation while ensuring human subject safety. We have identified three major points of concern: the potentially arbitrary 10% level proposed for safety assessment qualification of unique metabolites; the type and duration of the safety testing (safety testing vs. toxicity testing) to qualify unique metabolites; and the impact of these studies on increasing timelines and costs on the critical path of drug development.

We have also read and contributed to the comments submitted on behalf of PhRMA Drug Metabolism and Drusafe Committees. Rather than repeat many of their thoughts on the above three major points of concern, we would like to fully endorse these.

J&J believes that this current draft Guidance, together with PhRMA's MIST paper, is a very good starting point for more extensive discussions between the FDA and experts from the pharmaceutical companies in this extremely complex area. We are in favor of a continued collaborative effort between the Agency and the pharmaceutical companies to reach a consensus based on the science, as well as on the mutual goal of bringing safe new drugs to the patients as soon as possible. We welcome the opportunity to further work on this topic with the FDA.

The following additional, more specific, comments are listed below.

Although we recognize that a value is needed to define a major metabolite, our experience suggests that most of the time 10% is overly conservative (from a toxicity or activity standpoint). Also, from a practical standpoint, ability to define and pursue this value is technically very

difficult and often unattainable. Therefore, we suggest that the initial qualification level for more detailed characterization be 25%.

In the section pertaining to the conduct of general toxicity studies using the metabolites, the agency recommends studies varying between 14 to 90 days. We don't think that these should be conducted as standard toxicology studies with MTD determined, but rather as safety studies, i.e., at some multiples of the human exposure. Pushing metabolites to unrealistic doses resulting in unattainable plasma concentrations will often generate a misleading toxicology profile of no relevance to the clinical situation.

We feel very strongly that, similar to the FDA guidance on toxicity testing for impurities in drug substances, one species generally dosed for one (1) month is sufficient to characterize the potential toxicity of the unique or major human metabolite. To differentiate qualification of unique human metabolites from qualification of new impurities never tested in man would be inconsistent with the FDA's rationale used, approved, and in practice for qualifying unique impurities.

We also believe that administering a major metabolite(s) by the oral route is scientifically challenged and should be avoided whenever possible, especially when multiple metabolites are formed. Many times metabolites interact with each other generating complex mechanisms of toxicity or even tissue repair. Therefore, administering individual metabolites may produce very misleading results. Additionally, reactive metabolites cannot be administered directly as they cannot be obtained in stable form. Therefore, administering major metabolites up to MTD and chronically up to 90 days or more should be carefully evaluated and determined on a case-by-case basis rather than on a 10% rule basis.

The guidance document recommends using only in vivo animal models. Many times mechanistic information may be obtained from simple in vitro cytotoxicity studies in cell cultures and monitoring various biochemical parameters. These mechanistic data may be complementary to in vivo studies. Such data should be used to produce a scientific rationale in selecting doses and conducting general toxicity testing in animals. This mechanism-based approach, instead of a "generic" qualification program, is consistent with the principles outlined in the Stagnation or Innovation document published by FDA in 2004.

Strategically, this proposal may lengthen the "Critical Path" as published by the FDA in 2003. In order to avoid this, evaluation of human metabolites should be much more risk assessment driven (i.e., more assessment and less testing) based upon short-term testing in animal models. If anything longer is required, the benefit risk analysis should be made for patient safety to allow these animal studies to be done during Phase III, before NDA submission. The conduct of carcinogenicity studies should be the real exception.

The agency has recommended having the results of the toxicity studies completed and submitted before beginning large-scale Phase III trials. This will sometimes be difficult, or even impossible, especially if chronic toxicity studies are needed with the metabolite.

The draft guidance indicates several instruments, (GC/MS, LC/MS, MS/MS, etc.) which can be used for identification of metabolites with improved sensitivity. However, mass spectrometry can often miss some unusual metabolites and identification of such metabolites can sometimes be obtained only from radiolabel studies.

No clear distinction is made regarding stable versus reactive metabolites. The examples presented in lines 83 to 103 are agents that produce reactive metabolites. If a reactive metabolite is produced as a primary metabolite, i.e., directly from the drug, then such metabolites cannot be isolated in stable form. Only genotoxicity studies, covalent binding studies, or isolation of secondary metabolites of the reactive metabolites such as mercapturates/GSH conjugates may indicate the formation of such reactive metabolites. The assessment of toxicity for these metabolites can only be obtained from indirect evidence from the studies conducted by the parent drug.

On page 7, Section D, the Agency can require carcinogenicity studies with the metabolite. It is recommended to add a dose group with the metabolite to the oncogenicity study with the parent drug. What if there is an increase in tumor incidence with the metabolite? Since there is only one dose group, it will be difficult to draw conclusions. We would rather advise a separate study, preferably as a phase IV commitment, with the metabolite and include three (3) dose groups.

FDA recommends that sponsors contact the relevant review division to discuss the number of non-clinical studies for the unique or major human metabolites on a case-by-case basis, but only for drugs in development for serious or life-threatening diseases that lack an approved effective therapy. We feel that similar discussions should also be possible for other drugs in development.

Summary

In closing, we would like to thank the Agency, in advance, for its thoughtful consideration of our comments/recommendations. We hope the dialog between FDA and the pharmaceutical companies can continue to address the major points of concern raised by J&J and the other pharmaceutical companies, in order to reach a sufficient level of consensus on the safety testing of drug metabolites prior to the finalization of this Guidance. If we can provide further assistance, please do not hesitate to contact us at either (908) 704-4396 or (908) 704-4709.

Sincerely,
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Herman Van Cauteren, M.D.V.
Senior Vice President
Global Preclinical Development

Alfred P. Tonelli, Ph.D.
Vice President
Global Preclinical Development